UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	9

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/726,093	Fuchs et al.
Examiner	**Group Art Unit**
Ardin Marschel	1809

☒ Responsive to communication(s) filed on 5/7/97 and 6/6/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 32-67 is/are pending in the application.

~~Of the above,~~ Claim(s) 1-31 have been canceled. ~~is/are withdrawn from consideration~~.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 32-67 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, ~~Paper No(s).~~ 6 sheets

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

It is noted that the enclosed Examiner Interview Summary of 6/10/97, indicated that the previous office action, mailed 6/2/97, did not consider a preliminary amendment, filed 5/7/97, because it apparently crossed in processing with said previous office action. Accordingly, this office replaces said previous office action and additionally considers the amendment, filed 5/7/97, and the IDS, filed 6/6/97. The response time is hereby restarted as of the mailing date of this office action. Rejections and/or objections not reiterated from the previous office action are hereby withdrawn. The following rejections and/or objections are either newly applied or reiterated. They constitute the complete set presently being applied to the instant application.

The numbering of claims is not accordance with 37 C.F.R. § 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 C.F.R. § 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 39-74 have been renumbered as claims 32-67, respectively.

If applicant desires priority under 35 U.S.C. § 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant

application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38, 39, and 46-67 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. That is, NEW MATTER is present in claims 38, 54, and 66 in that the limitation of "particle" as associated with the PNA probe has not been found in the disclosure as filed. It is noted that "colored particles" are given in claim 3, as filed, as a detectable moiety that is attached to a PNA probe. Also, the specification at page 12, line 9, cites "resin-bound PNAs". Neither of these citations, however, give a written description of the generic limitation "particle" that is now in claims 38 and 54. Similarly, the "charge-modifying moiety" limitation; given now in claims 39, 55, and 64; has not been

found in the instant disclosure as filed. Consideration of the written description of the apparatus of the invention as filed has failed to reveal written support for the apparatus including a denaturing reagent as cited as part c) of instant claims 46 and 58 and claims dependent therefrom. Therefore, the instant apparatus claims 46-67 that include said denaturing reagent contain NEW MATTER. The apparatus disclosures that have been found as filed are in the originally filed claims and in the specification at page 5, lines 13-22. An additional NEW MATTER limitation is given in instant claims 58-67 in that claim 58, part b), cites a sample that comprises both a double stranded polynucleotide and at least one PNA probe. It is noted that this sample also is also disposed to mix with "at least PNA probe" given in the first line of said part b) of claim 58. This is NEW MATTER in that a PNA probe is both in the sample as well as in the apparatus with the apparent intention to be mixed with the PNA containing sample.

Claims 36 and 46-67 are rejected, as discussed below, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In part b) of claim 58 the wording is unclear as to whether the sample contains both a double stranded polynucleotide and a PNA probe that is separate from the PNA probe that is in the apparatus that is disposed to be mixed with said sample or whether the sample only contains a double stranded polynucleotide

and the PNA probe is merely being characterized in the last 2 lines of said part b). Clearer claim wording is requested to remove this unclarity. It is noted that one interpretation is that this may be NEW MATTER as discussed in the above rejection.

In claim 36 "the medium" is cited without antecedent basis in claim 32 from which claim 36 depends thus making claim 36 vague and indefinite as to what is meant thereby.

Claims 46-67 are vague and indefinite regarding the metes and bounds that are intended for the mixing practice cited in part b) of independent claims 46 and 58. Said part b) sections both cite the presence of an introduction zone as well as the presence of a PNA probe that is disposed to mix with a sample. Two possible interpretations of the claim wording are as follows: Firstly, the mixing of the PNA probe with the sample is limited to being performed in said introduction zone. Secondly, the sample is introduced per se into the apparatus in the introduction zone but that the PNA probe may be mixed in any zone or channel anywhere in the apparatus. Clarification is requested as to the metes and bounds regarding the introduction zone versus the PNA probe mixing practice.

In claim 46, line 1, the use of the claimed apparatus is given as "An apparatus for detecting...". Claim 46 then lists several limitations such as a sample introduction zone etc. but confusingly lacks any detection zone or apparatus limitation that directs the apparatus for detection per se. This causes claims 46-55 and 57 to be vague and indefinite as to whether an

apparatus that is utilized only to separate assay component such as complexes is within the scope of the claims or whether the claimed apparatus must include a feature that results in detection as cited in above line 1 of claim 46. Clarification as to the metes and bounds of the claimed apparatus regarding the detection wording in the preamble is requested.

In claim 58, line 4, the phrase "at least PNA probe" is given. This phrase is unclear as to what "at least PNA" is meant to be. It is noted that similar wording is given in claim 46, line 4, and that claim 58 may simply be missing the word "one" as a typographical error.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 32, 33, 35-37, 39, 40, 42-47, 50-53, 55, and 56 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Rose.

Rose discloses the separation of PNA/nucleic acid complexes from hybridized nucleic acid/nucleic acid duplexes by capillary

electrophoresis as well as capillary electrophoretic apparatus for performing said separation that reads on the above claims. The PNA displaces its complementary oligonucleotide from a DNA duplex and is shown in Figure 7 on page 3549 as being separated from the other components in the mixture. This is also described on page 3549, second column, first full paragraph. The PNAs are detectably labeled via nucleobases that are detectable by 260 nm absorbance. The buffer conditions of the procedure inherently contain denaturing reagent(s) due to the duplex denaturation that occurs as evidence thereof. The PNA that is depicted on page 3546 of the reference contains a charge-modifying moiety as given in instant claim 39 in that the upper terminus of the structure contains an amine moiety that results in a normally present "plus" charge that is modified compared to the terminus without this amine moiety which would be a carboxyl which is normally negatively charged. This charge modification is also discussed on page 3546 in the sentence that bridges the first and second columns. The reference's capillary contains a sieving medium as is also a limitation of instant claim 40.

Claims 32-39, 44, and 45 are rejected under 35 U.S.C. § 102(b) and (e) as being clearly anticipated by Summerton et al.

Summerton et al. disclose hybridization assay procedures wherein PNA polymers replace nucleic acid probes targeted to single stranded sample nucleic acid as discussed in column 3, line 63, through column 4, line 43. The PNA polymers contain various types of bases including natural bases as noted in column

16, lines 14-41. The PNA molecules are disclosed as optionally containing negative charges in column 16, lines 49-53, which reads on the charge-modifying limitation of instant claim 39. Section VIII in columns 21-24 disclose the basic assay steps including probe/target complex detection as discussed, for example, in column 23, lines 49-68. Figure 7 depicts the PNA polymers wherein the R groups contain nucleobases for hybridization to target nucleic acid. The hybridization or annealing reaction portion of the assay of Summerton et al. is disclosed as including denaturants such as formamide as discussed in column 22, lines 41-61. Summerton et al. also discloses the attachment of the PNA probe to a solid support such as a bead-particle in column 18, lines 17-56. The assay includes washing or separating bound (probe/target complex) from unbound probe as part of the detection process in column 22, line 62, through column 23, line 4, as well as in column 23, lines 49-52. A low salt annealing buffer is added for ionic strength adjustment in the assay as described in column 22, lines 1-10, as is also a limitation of instant claim 35. Temperature adjustment for hybridization must inherently occur because the sample is chilled as described in column 21, lines 64-66, and then subjected to annealing with the probe as stated in column 22, lines 20-40. Both the chilling and the annealing reactions occur via temperature adjustments as well as between these steps as is also instantly claimed in claim 36. Column 51, lines 16-29, of Summerton et al. disclose the added feature that multiple species

of polymer may be utilized so as to bind to different target polynucleotides from different analytes, complementary target strands, or different analyte segments to increase the sensitivity of detection of a single duplex analyte which are reasonably interpreted as limitations of instant claims 44 and 45 wherein multiple PNA probe practice is cited. Lastly, it is noted that page 9 of the instant specification depicts a particular PNA structure but that lines 3-9 of said page 9 broadly defines PNAs and does not limit them to said depicted backbone structure. Therefore, the PNAs cited in the instant claims are not limited as to any particular PNA backbone structure type and thus broadly include the structures as cited in Summerton et al. within their scope of PNA practice.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a),

the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 46, 49-58, and 61-67 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wilding et al.(P/N 5,498,392), taken in view of Summerton et al.(P/N 5,217,866).

Wilding et al. disclose an apparatus which is a basic microchip device that is utilized for nucleic acid manipulations including sample preparation on the chip inclusive of cell lysis, processing to perform PCR, and detection of PCR product. The detection of the products of PCR amplification is motivated and suggested, for example, in column 11, lines 56-67, as being via hybridization techniques that are known in the art. The processing of nucleic acids for PCR includes dehybridization of double stranded nucleic acids in column 3, lines 39-60. This dehybridization is also accompanied by temperature control as needed to "melt" the double stranded nucleic acids in the sample. This dehybridization of sample nucleic acids is a well known technique in the art and is known to be performed by denaturation of the nucleic acids as is also identically required so as to permit the binding of a PNA molecule to a complementary single stranded nucleic acid during the instantly claimed PNA hybridization assays practice of the claimed apparati. An inlet port is utilized to introduce the sample for analysis into the

microchip flow system as noted in column 4, lines 3-9, and may be termed a sample introduction zone as instantly claimed. Reagents as required for assay performance are present in the apparatus microchip by injection through inlet ports or via capillary action as described in column 4, lines 13-28, and in column 7, lines 42-45. Such capillary action also discloses the capillary limitations as given in the instant claims. The performance of multiple assays on a single chip is disclosed in Table 1 in column 6, lines 12-14, and in column 5, lines 9-11. The flow channels are capillaries as described in column 7, lines 46-53, via the sizes therein disclosed as well as in the Figures that depict these channels as a parallel walled flow system corresponding also to the characteristics of a capillary. These channel and multiple assay disclosures combine to result in meeting the instant claim 58 limitation in line 1 of a "plurality of capillary channels". Wilding et al. suggests and motivates the purification of a polynucleotide probe on a bead (or as instant termed a particle) that is bound to target amplified polynucleotide in column 5, lines 27-38, which may be termed a separation zone as instantly claimed since purification includes the separation of components from each other. This separation zone is in the microchip flow system and thus in communication as cited in part e) of instant claim 58. A detection zone is disclosed as being in the microchip device as a means of detecting amplified polynucleotides as cited in column 8, lines 12-16. Wilding et al. lacks the disclosure of a denaturing

reagent and a PNA probe in the microchip. As noted above, the reference, however, does suggest and motivate the practice of hybridization assay techniques that were known in the art as well as the introduction of reagents as needed onto the microchip. The following reference discloses such standard methods directed to PNA polymer probes and denaturant usage in hybridization assays.

Summerton et al. disclose hybridization assay procedures wherein PNA polymers replace nucleic acid probes that are targeted to single stranded sample nucleic acid as discussed in the bridging paragraph between columns 3 and 4. Figure 7 depicts the PNA polymers wherein the R groups contain nucleobases for hybridization to target nucleic acid. These PNA polymers are motivated by overcoming problems in the prior art regarding hybridization assays as noted in column 2, lines 5-9, as the object of the invention of Summerton et al. The PNA polymers contain various types of bases including natural bases as noted in column 16, lines 14-41. The PNA molecules are disclosed as optionally containing negative charges in column 16, lines 49-53, which reads on the charge-modifying limitation of instant claims 55 and 64. Section VIII in columns 21-24 disclose the basic assay steps including probe/target complex detection as discussed, for example, in column 23, lines 49-68. The hybridization or annealing reaction portion of the assay of Summerton et al. is disclosed as including denaturants such as formamide as discussed in column 22, lines 41-61, as is also a

limitation of instant claims 49 and 61. Summerton et al. also discloses the attachment of the PNA probe to a solid support such as a bead-particle in column 18, lines 17-56, as is also given in instant claims 54 and 66. The assay includes washing or separating bound (probe/target complex) from unbound probe as part of the detection process in column 22, line 62, through column 23, line 4, as well as in column 23, lines 49-52. A low salt annealing buffer is added for ionic strength adjustment in the assay as described in column 22, lines 1-10, as is also a limitation of instant claims 50 and 62. Summerton et al. disclose a reporter system that detectably labels the PNA/target complex as is summarized in column 18, line 57, through column 21, line 10. This reporter is utilized as described in the method in column 23, lines 5-10, for detection practice.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the instant invention because Wilding et al. discloses basic microchip apparatus limitations including a flow system with an introduction zone, separation zone, and detection zone with reagent inlet port(s) and also motivates and suggests any generic hybridization binding assay performance as known in the prior art which is deemed to include the improvement of Summerton et al. which discloses a PNA binding assay for nucleic acid targets in a sample that is usable with denaturants such as formamide. Both Summerton et al. and Wilding et al. disclose particle attachment to probes that are practiced in separation methodology and

associated apparati features.

Claims 32-37, 39-53, 55, and 56 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rose taken in view of Chen et al. (Ref. CN).

Rose has been summarized above but lacks disclosure of the practice of gel in the capillary electrophoresis apparatus as containing polyacrylamide as given in instant claims 41 and 48. Rose, however, suggests and motivates generic capillary electrophoresis on page 3546, first column, lines 3-8, as being of the type also utilized for DNA-DNA duplex analysis as given in Chen et al. (Ref. CN).

Chen et al. (Ref. CN) discloses capillary electrophoresis therein as utilizing polyacrylamide filled gel capillaries as given in the abstract and on page 296, last paragraph, and in Figure 1 on page 299. It is noted that Chen et al. also suggests and motivates the use of urea as a denaturant of double stranded nucleic acids on page 298 in the section entitled "Dissociation of the hybridized species by urea and heat" as also given in instant claims 34 and 49.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the instant invention because Rose gives the basic method and apparatus and suggests and motivates, by specific reference, the capillary gel electrophoresis methodology of Chen et al. (Ref. CN) as being the type of electrophoretic practice therein being investigated. Chen et al. (Ref. CN) discloses both capillary

electrophoresis as being performed with polyacrylamide in the capillary gel and optionally urea for denaturation.

Fuchs et al. (P/N 5,630,924) is cited on the enclosed PTO Form 892 as being of interest due to citing similar subject matter to the instant application and one common inventor.

Enclosed is an executed PTO Form 1449 with citation EJ thereon lined through because it is not a published document and therefore does not have a date of publication. Also, reference EQ is lined through because it was previously cited on a PTO Form 892 to avoid duplication of citation as having been considered.

The disclosure is objected to because of the following informalities:

In the specification on page 8, line 22, the word "completmentary" appears to be misspelled.

Appropriate correction is required.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4227 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

August 14, 1997

Ardin H. Marschel

ARDIN H. MARSCHEL
PRIMARY EXAMINER
GROUP 1800